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[Claim 14 has been amended as follows:]

14. (Twice Amended) A method according to claim 13 wherein said metallocene is ferrocene.

#### REMARKS

Claims 2-11, 13-15 are pending. An appendix with the pending claims is attached for the Examiner's convenience.

As a preliminary matter, claim 5 has been included in the "Version with Markings to Show Changes Made" to correctly indicate the term "is" was replaced. In addition, the Examiner notes that claim 7 has not been amended as suggested by the inclusion of claim 7 in the "Version with Markings to Show Changes Made". Applicants apologize for the inadvertent inclusion of claim 7 in this section, as there was no intention on the applicants part to make amendments to claim 7.

#### The Invention:

The present invention is directed to methods of making modified nucleosides. The methods comprise reacting an anhydro-nucleoside with a primary amine on an electron transfer moiety with a primary amine in the presence of an activation agent. The electron transfer moieties may be attached to either the 2' or 3' position of the ribose.

The choice of which anhydro-nucleoside to use depends on where the electron transfer moiety is to be attached. If the electron transfer moiety is to be attached to the 2' position of the ribose of a pyrimidine nucleoside, a 2,2' anhydro-nucleoside is used. For attachment to the 3' position of the ribose of a pyrimidine nucleoside, a 2,3' anydro-nucleoside is used. Similarly, anhydro-nucleosides also can be made by forming a bridge between the N-3 of the purine and the 2', 3' or 5' position on the ribose.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 2-11 and 13-4 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. The Examiner restates his position that without complete chemical structures, "functional terms of the kind quoted have meanings which may be read to include a vast array of subject matter not included within the disclosure and are therefore lacking in the degree of precision expected in view of 35 U.S.C. § 112, second paragraph".

Applicants restate their position that when the subject matter of the invention relates to a process, a claim need only recite the necessary steps. There is no requirement that a structure be disclosed in a method claim. *Dennison Mfg. Co. v. Ben Clements & Sons, Inc.*, 467 F. Supp. 391, 203 USPQ 895 (1979, SD NY). An example of a method patent in which only the necessary steps for making a class of chemical compounds is U.S. Patent No. 6,043,061.

Accordingly, the rejection is improper and should be withdrawn.

Rejection of Claim 7 under 35 U.S.C. § 112, second paragraph

Claim 7 is rejected for using the term "comprising". The Examiner restates his position that it is incorrect to use the word comprising when claiming a chemical structure.

Applicants maintain that comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. In *Genetech, Inc. v. Chiron Corp.*, 112 F.3d 495 (Fed. Cir. 1997). The use of "comprising" is not restricted based on the nature of the material being claimed, rather it is the prior art that determines whether an open ended term such as "comprising" is appropriate.

Thus, in *Ex parte Sawyer* (1961, Bd App) 130 USPQ 476, where an Examiner had rejected a claim because of the use of "comprising", the Board held:

There is no prior art which necessitates restriction of the claims. The examiner also felt the term consisting essentially of should be used. We see no need in the absence of pertinent art why the claims should be so restricted as it is obvious that a wide variety of materials may be thickened

with the claimed composition and various inert materials may be added to the composition without destroying the same or materially affecting its function.

Similarly, In *In re Baxter*, 210 U.S.P.Q. 795, 802-803 (C.C.P.A. 1981), the court in interpreting the following claim "A process which comprises interpolymerizing monomers comprising ethylene and propylene in the presence of . . ." stated:

In the absence of ambiguity, it is fundamental that the language of a count should be given the broadest reasonable interpretation it will support and should not be given a contrived, artificial, or narrow interpretation which fails to apply the language of the count in its most obvious sense. . . . Bearing in mind the above considerations and recognizing that Baxter's proposed count A is a comprising-type count, we are satisfied that the scope of the proposed count includes polymerizing propylene with any other monomer (copolymerization), such as ethylene, as well as homopolymerization. As long as one of the monomers in the reaction is propylene, any other monomer may be present, because the term "comprises" permits the *inclusion* of other steps, elements, or materials.

Applicants submit that the present specification supports the use of "comprising" because compounds which may serve as electron transfer moieties are defined on pages 7-8; compounds which contain primary amines are defined on page 6, and methods for making a 2' modified nucleoside comprising an electron transfer moiety and a primary amine are disclosed on pages 18-20, Example 1, and Figures 2 and 3. Furthermore, the Examiner has provided no prior art which warrants a narrowing of the claim language.

Accordingly, applicants submit that it is not incorrect to use the term "comprising" in this context and respectfully request withdrawal of the rejection of Claim 7 under 35 U.S.C. § 112, second paragraph.

In addition, the Examiner has reiterated his rejection of Claim 7 for using generic terms with many possible structural meanings and for using terms which are meaningless unless the details of the chemical reaction are provided. Specifically, the Examiner rejects the use of "anhydronucleoside", "electron transport moiety", "activated anhydronucleoside", "cyclization agent" and "cyclized intermediate".

To reiterate section 2173.05(a) of the M.P.E.P., "the meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed". As argued previously, terms such as "anhydro-nucleoside" and "nucleoside analog" are art recognized terms. For example, one of the references provided by the Examiner, Nexstar '102, refers to cyclization reactions (see page 3, line 29 through page 4, line 3); analogs of nucleosides (see page 1, lines 25 and 27); and anydronucleosides (see page 21). Other references, such as Sebesta, et al., *Tetrahedron*, (1996) 46:14385-14402, cited by the Examiner, use the terms nucleoside analogs and anhydronucleosides without further definition. See for example, the title, last sentence of the abstract, first sentence of the introduction, first sentence of the background, and throughout the entire paper.

In addition, the Applicant has defined what is meant by each of these terms in the application and drawings. According to M.P.E.P. § 2173.05(a), "when the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning." Applicants note the Examiner's statement that the definition of electron transfer moiety does not meet the standard of 35 U.S.C. § 112, second paragraph because the definition is entirely functional, the definition includes the term grammatical equivalents, and the definition fails to limit the subject matter to any specific compounds.

Applicants submit that the general definition of electron transport moiety found at page 7, lines 13-25 combined with the list of preferred electron transport moieties found on page 7, line 24 through page 11, line 9, fully comports with the standard of U.S.C. § 112, second paragraph.

To reiterate, the general definition of electron transfer moiety is found at page 7, lines 13-25 of the specification:

By the terms "electron donor moiety", "electron acceptor moiety", and "electron transfer moieties" or grammatical equivalents herein refers to molecules capable of electron transfer under certain conditions.

Beginning on page 7, line 24 through page 11, line 9, descriptions of preferred electron transport moieties are found. For example, the following list of electron transfer moieties is found on page 8, lines 1-10:

In a preferred embodiment, the electron transfer moieties are transition metal complexes. Transition metals are those whose atoms have a partial or complete d shell of electrons. Suitable transition metals for use in the invention include, but are not limited to, cadmium (Cd), copper (Cu), cobalt (Co), palladium (Pd), zinc (Zn), iron (Fe), ruthenium (Ru), rhodium (Rh), osmium (Os), rhenium (Re), platinum (Pt), scandium (Sc), titanium (Ti), Vanadium (V), chromium (Cr), manganese (Mn), nickel (Ni), Molybdenum (Mo), technetium (Tc), tungsten (W), and iridium (Ir). That is, the first series of transition metals, the platinum metals (Ru, Rh, Pd, Os, Ir and Pt), along with Fe, Re, W, Mo and Tc, are preferred. Particularly preferred are ruthenium, rhenium, osmium, platinum, cobalt and iron.

Definitions for "anhydronucleoside" and "activated anhydronucleoside" also are provided in the specification. For example, "anhydronucleoside" is defined as a "2,2'-, 2,3'- or 2,5' anhydronucleoside, comprising an oxygen bridge between the C-2 of the base pyrimidine and the C-2' or C-3' of the ribose or ribose analog." See specification at page 18, line 23 through page 19, line 13. An "activated anhydronucleoside" is formed when an anhydronucleoside and a signalling moiety comprising a primary amine are added together in the presence of an activation agent. See page 20, lines 1-2. On page 20, lines 10-11, an "activated anhydronucleoside" is defined as an "anhydronucleoside ready to react with the signalling moiety comprising a primary amine to form a carbamate."

The Examiner states that the terms "cyclization agent" and "cyclized intermediate" are meaningless because the details of the chemical reaction are not provided. Applicants wish to draw the Examiner's attention to Figures 1 and 2. In Figure 1 a generalized scheme for making modified nucleosides is illustrated. In Figure 2, specific details of the reaction are included. Specifically, reaction e) demonstrates the formation of a cyclized intermediate in the presence of a cyclization agent.

Accordingly, applicants submit the terms "anhydronucleoside", "electron transport moiety", "activated anhydronucleoside", "cyclization agent" and "cyclized intermediate"

are either art defined terms or are defined in the specification. Applicants request withdrawal of the rejection.

*Rejection of Claim 2 under 35 U.S.C. § 112, second paragraph*

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, because it is allegedly unclear as to how the phosphoramidite group is added. Applicants refer the Examiner to page 21, lines 1-22, which describes how a phosphoramidite group may be added to the 3' position of a 2'-modified nucleoside. Applicants submit that a person of skill in the art, using the description provided would know how the phosphoramidite group is added. Accordingly, applicants request withdrawal of the rejection.

*Rejection of Claim 3 under 35 U.S.C. § 112, second paragraph*

The Examiner restates his position that claim 3 is indefinite for failing to specify the chemical structural variables which define the phosphoramidite modified nucleoside. Applicants submit that the amendment made to Claim 2 in the previous office action clarifies that the phosphoramidite moiety is added to the 3' position of the nucleoside. In addition, applicants draw the Examiner's attention to Figure 3, reaction h), which illustrates a phosphoramidite-derivatized nucleoside as disclosed in Claim 3.

As argued previously, the specification on page 21, lines 15-22 makes it clear that the phosphoramidite modified nucleotide that results is known in the art. In *In re Sneed*, the court held "claims in an application are to be given their broadest reasonable interpretation consistent with specification, and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Sneed*, 710 F.2d 1544,1548 (1983). As the Examiner notes, the specification makes reference to the Caruthers process of nucleic acid synthesis. See specification page 21, lines 21-22. Thus, the phosphoramidite modified nucleoside referred to is known to one of ordinary skill in the art and does not require further elucidation. Accordingly, the rejection should be withdrawn.

*Rejection of Claim 5 under 35 U.S.C. § 112, second paragraph and 35 C.F.R. § 1.75(c)*

The Examiner restates his rejection of Claim 5 for the use of the term "nucleoside analog". Applicants restate their position that "nucleoside analog" is an art recognized term as evidenced by the numerous references describing nucleic acid analogs which have been incorporated by reference and are listed in the specification at page 4, line 2 through page 5, line 4. Accordingly, applicants submit the specification combined with the prior art provides sufficient guidance to permit the ordinary practitioner to determine which compounds qualify as a "nucleoside analog". Applicants respectfully request withdrawal of the rejection.

*Rejection of Claim 6 under 35 U.S.C. § 112, second paragraph*

Claim 6 has been amended to correct the spelling of the term "carbonyldimidazole" to its proper spelling "carbonyldiimidazole". Accordingly, the rejection should be withdrawn.

*Rejection of Claim 8 under 35 U.S.C. § 112, second paragraph*

Claim 8 is rejected for allegedly using entirely functional language. Additionally, the Examiner notes that the claim as written "refers to both compounds and substituents, appearing to equate the two, a clear technical error." Applicants disagree.

Applicants, relying on the definition provided in the specification on page 8, lines 1-18, have claimed an electron transfer moiety that is a transition metal complex. As outlined in the specification on page 8, lines 11-15, a transition metal complex comprises a metal ion and a ligand. The exact number of ligands will depend on the choice of the metal. As someone of skill in the art would be able to determine the coordination atoms for the binding of one of the transition metals, applicants submit that a person of skill in the art would also be able to determine the number of ligands required based on the information provided in the specification. Accordingly, the rejection should be withdrawn.

*Rejection of Claim 9 under 35 U.S.C. § 112, second paragraph*

The Examiner rejects Claim 9 because it is allegedly technically incorrect and incomplete because the structures of the transition metal complex must include other components. Applicants respectfully disagree.

Claim 9 is directed to a subset of preferred transition metals that may be incorporated into a transition metal complex. Applicants submit that so long as a dependent claim includes every limitation of the claim on which it depends and is more restrictive, a subset of the one of the elements listed may be claimed in the dependent claim (M.P.E.P. § 608.01(n)). As Claim 9 depends from Claim 8 which lists both the transition metal and the ligand, Claim 9 includes the limitation of the transition metal and the ligand. In addition, Claim 9 is more restrictive in that a subset of transition metals are claimed. Accordingly, applicants request withdrawal of the rejection.

*Rejection of Claim 10 under 35 U.S.C. § 112, second paragraph*

Claims 10 and 11 are rejected for allegedly using functional language that only hints at the structure of the intended product.

Specifically claim 10 is rejected for using the term polydentate ligand. Applicants submit that the term "polydentate ligand" is a term of art that refers to a ligand having two or more donor atoms. Suitable polydentate ligands of use in the invention are disclosed in Figure 2, the product resulting from step f) and in Figure 3, the product resulting from step h).

As can be seen from Figures 2 and 3, a polydentate ligand has the general form  $R_1-X-R_2$ , wherein  $R_1$  and  $R_2$  are sigma donors. Accordingly,  $R_1$  can be a primary amine (see specification at page 6, lines 8-11; page 8, line 24), X may be a linker moiety that serves to covalently link the R groups in a conformation suitable for binding to the transition metal (see specification at page 6, lines 18-21), and  $R_2$  can be another N donating moiety (see page 8, line 21 through page 9, 11). Accordingly, applicants submit that the use of the term "polydentate ligand" is not indefinite and request that the rejection be withdrawn.



*Rejection of Claim 11 under 35 U.S.C. § 112, second paragraph*

Claim 11 is rejected for using the term “coordination atom” because the term allegedly does not specify the overall structure of the ligand being claimed. As the Examiner is aware, Claim 11 depends from Claim 10 which is drawn to methods of making a transition metal complex. Claim 11 serves to define one aspect of the transition metal complex, that is the donor atoms that comprise the polydentate ligand. Appropriate donor atoms for a polydentate ligand that is a sigma donor those listed in the claim and supported by the specification at page 8, lines 19-22. Accordingly, applicants request that the rejection be withdrawn.

*Rejection of Claims 13 and 14 under 35 U.S.C. § 112, second paragraph*

Claims 13 and 14 are rejected for using terms allegedly inconsistent with the terms used in Claim 10. Claims 13 and 14 have been amended to be consistent with the language used in claim 10. As amended, claims 13 and 14 are directed to making the transition metal complex of in claim 10 using a different ligand and metal. Accordingly, applicants request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 2-11 and 13-15 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner argues that “the chemical reactants are described using generic terms only” and that the applicants “disclose only a limited number of specific embodiments, leaving the ordinary practitioner the unreasonable burden of determining which claimed embodiments are actually operative and which are not.” Applicants respectfully disagree.

It is well settled law that the specification must enable the scope of the claimed invention, but that the specification need not provide a specific description for each and every embodiment covered by the claimed invention. *See, e.g., Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). That the claimed invention covers a wide variety of compounds amenable to synthesis in accordance with the claimed

invention is not relevant to the issue of enablement. Rather, the test of enablement requires that the specification, in light of the prior art, provides ample guidance to one of skill in the art, to make and use the compounds of the invention. Applicants maintain that the specification provides specific examples of making at least two modified nucleosides comprising transition metal complexes. For example, the example provided teaches the synthesis of a the polydentate ligand shown in Figure 2, Figure 3 depicts the synthesis of a transition metal complex; the methods for making are described in the specification at page 18, lines 6-16; page 18, line 23 through page 20, line 21. This alone is sufficient teaching to enable the scope of claims 2-11 and 13-15. Accordingly, applicants request withdrawal of the rejection

Rejection Under 35 U.S.C. § 103(a)

Claims 2-11 and 13-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nexstar.

The Examiner restates his position that the Nexstar reference discloses processes for making labeled nucleoside from anhydro-nucleosides wherein the label is an electron transfer moiety. Applicants respectfully disagree.

The Nexstar reference teaches a method for making modified nucleosides. However, the Nexstar reference does not teach the synthesis of nucleosides modified at the 2' position with a transition metal complex.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. See, e.g., *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The

teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

Claims 2-11 and 13-14 are directed to methods of making nucleosides modified with electron transfer moieties. Preferably, the electron transfer moiety comprises a transition metal coordinately bonded to one or ligands. See for example the specification at pages 7-11. Further, a primary amine must be an integral part of the electron transfer moiety prior to its addition to the nucleoside. See specification at page 6, lines 8-14.

As argued previously, the Nexstar reference teaches a method for making modified nucleosides that does not include coordinate-covalently bonded metal atoms or ions. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness against Claims 2-11 and 13-14. Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 2-11 and 13-14 under 35 U.S.C. § 103(a) as being obvious over Nexstar as a *prima facie* case of obviousness has not been made.

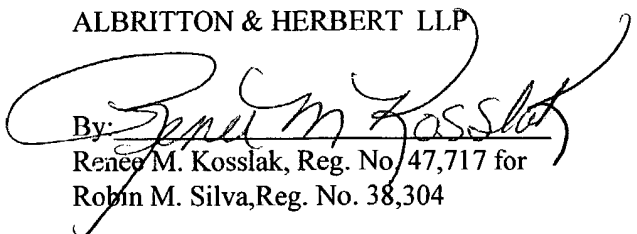
Applicants submit the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Dated: 11/2/01

Respectfully submitted,

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